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A propensity score-matched analysis of mortality in solid organ transplant patients with COVID-19 compared to non-solid organ transplant patients

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Abstract

In the context of COVID-19 pandemic, we aimed to analyze the epidemiology, clinical characteristics, risk factors for mortality and impact of COVID-19 on outcomes of solid organ transplant (SOT) recipients compared to a cohort of non transplant patients, evaluating if transplantation could be considered a risk factor for mortality. From March to May 2020, 261 hospitalized patients with COVID-19 pneumonia were evaluated, including 41 SOT recipients. Of these, thirty-two were kidney recipients, 4 liver, 3 heart and 2 combined kidney-liver transplants. Median time from transplantation to COVID-19 diagnosis was 6 years. Thirteen SOT recipients (32%) required Intensive Care Unit (ICU) admission and 5 patients died (12%). Using a propensity score match analysis, we found no significant differences between SOT recipients and non-transplant patients. Older age (OR 1.142; 95% [CI 1.08–1.197]) higher levels of C-reactive protein (OR 3.068; 95% [CI 1.22–7.71]) and levels of serum creatinine on admission (OR 3.048 95% [CI 1.22–7.57]) were associated with higher mortality. The clinical outcomes of SARS-CoV-2 infection in our cohort of SOT recipients appear to be similar to that observed in the non-transplant population. Older age, higher levels of C-reactive protein and serum creatinine were associated with higher mortality, whereas SOT was not associated with worse outcomes.

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Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in December 2019 in China rapidly evolving to the Coronavirus Disease 2019 (COVID-19) pandemic [1]. Reported associated mortality is around 7%, mostly related to older age, obesity, hypertension and chronic pulmonary disease [2].

Emerging data of the impact of COVID-19 in immunosupressed patients, including solid organ transplant (SOT recipients) has recently become available [3–18]. SOT recipients may be at a greater risk for worse outcomes due to the detrimental effect of the immunosuppressive therapy, similar to other viral infections, however, while some studies reflected poorer outcomes [6,9,16–18], other studies do not suggest worse prognosis compared to the non-transplant population [3–5,7,8,15,19].

Furthermore, besides immunosuppressive regimens, transplant recipients usually present more co-morbidities such as hypertension and diabetes, possibly influencing the outcome of patients with COVID-19. On the other hand, a propensity score match analysis has not been performed to assess mortality of solid organ recipients compared to non-solid organ transplant patients before.

In this setting, we aimed to study the epidemiology, clinical characteristics and mortality risk factors of SOT recipients that required hospitalization due to COVID-19 compared to a cohort of non transplant patients hospitalized in the same period, using a propensity score match analysis.

Material and methods

Patient selection

From 6th of March to 24^{h} of May, data regarding epidemiology, clinical and laboratory findings and outcomes of patients admitted with respiratory symptoms and radiological evidence of SARS-CoV-2 pneumonia to Hospital Clinic of Barcelona was prospectively recorded. We included all hospitalized patients.

Clinical data and definitions

Laboratory diagnosis of SARS-CoV-2 infection was made by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay from a nasopharyngeal swab.

We used the World Health Organization clinical Ordinary Scale Determination (OSD) to assess patient clinical status. This OSD was recorded at baseline and every day while hospitalization. The ordinal scale categories are as follows: 0) Uninfected 1) Ambulatory patients with no limitation of activities 2) Ambulatory patients with limitation of activities, 3) Patients requiring hospitalization in a non-ICU ward not requiring supplemental oxygen, 4) Patients requiring hospitalization in a non-ICU ward requiring supplemental oxygen, 5) Patients hospitalized in ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen, 6) Patients hospitalized in ICU requiring intubation and mechanical ventilation, 7) Patients hospitalized in ICU, requiring Extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy) and 8) Death during hospitalization.

The following laboratory measurements were recorded: Total lymphocyte count (cell/mm), serum C-reactive protein (mg/dL) (NR<0, D- dimer (ng/mL) (NR<500), serum Lactate dehydrogenase (IU/mL) (NR<234), serum Creatinine, (mg/dL) (NR 0.3–1.3), serum Ferritin (ng /mL) (NR 20–400), serum Troponin (ng /mL) (NR <42.2). For the purpose of statistical

analysis, the highest value recorded during hospitalization was used. For the total lymphocyte count the lowest laboratory value was selected for analysis purposes.

Streptococcus pneumoniae co-infection was considered if cultures from respiratory tract samples or urinary antigen were positive together with a chest X-ray or CT-scan suggestive of bacterial pneumonia.

All patients are prescribed prophylactic anticoagulation with enoxaparin 40 mg/24h unless contraindicated. Patients with overweight (>80Kg), D-dimer >3000 ng/mL, or with additional risk factors (cancer, history of thrombosis, recent surgery, etc) are prescribed enoxaparin 60 mg/24h unless contraindicated. In patients with clinical suspicion of pulmonary embolism a chest-CT is performed.

Cryptogenic Organizing pneumonia (COP) was defined on chest CT by multifocal ground glass opacities and/or consolidation.

Biopsy proven acute rejection episodes were recorded in the 3 months prior to admission.

All patients were followed-up after discharge for 2 months.

Treatment protocol

Our hospital protocol consisted of lopinavir/ritonavir 400/100 mg BID for 7–14 days plus hydroxychloroquine 400 mg/12h on the first day, followed by 200 mg/12h for the next 4 days. Patients with major drug interactions did not receive lopinavir/ritonavir. From the 18th of March, azithromycin 500 mg the first day and 250 mg/24h for 4 additional days was added to the regimen. All patients received prophylactic doses of heparin. The local indication of anti-cytokine therapy was for patients with pneumonia, progressive respiratory failure (increasing fraction of inspired Oxygen) and C-reactive protein (CRP) $\geq$ 8 mg/dL or ferritin $\geq$800 ng/mL or lymphocyte count < 800 cells/mm^3.

Choice of anti-cytokine therapy was at the discretion of the attending physician. Available anti-cytokine therapy in our center included: tocilizumab, anakinra and barticinib. Remdesivir therapy was prescribed if patients presented with: a) 7 days of symptoms or less, b)room air oxygen saturation of < 94%, c) glomerular filtration >30 (mL/min), and d) liver function tests < 5 times the upper normal limit according to Spanish Protocol from AEMS (Spanish Agency of Drugs and Heath Products) in addition to the standard of care. Hepatitis B serologies (hepatitis B surface antigen) and QuantiFERON-TB® were performed prior to anti-cytokine prescription and prophylaxis with entecavir and isoniazid were prescribed if applicable.

Immunosuppressive protocol

At baseline transplant patients could either be in a: a) calcineurin inhibitors based regimen (including tacrolimus or cyclosporine plus a cycle cell inhibitor and prednisone) or b) mTOR based regimen (including everolimus or sirolimus plus cycle cell inhibitor and prednisone).

According to center policy, due to the potential severity of SARS-CoV-2 infection, mycophenolate and mTOR inhibitor (mTORi) (Sirolimus or everolimus) were initially withdrawn in all admitted SOT recipients with COVID-19. Furthermore, in those patients starting treatment with lopinavir/ritonavir, the calcineurin inhibitor (CNI) (tacrolimus or cyclosporine) was also temporary discontinued due to the strong significant increase of CNI levels. Maintenance immunosuppression consisted of prednisone monotherapy (10–20 mg/day) until COVID-19 resolution, at which time tacrolimus was reinitiated at reduced doses (through blood levels around 5 ng/mL).

Statistical analysis

In the comparative analysis, we used the chi-square test with Yate's correction for categorical variables. Depending on their homogeneity, continuous variables were compared using the *t* test or Mann-Whitney test. Statistically significant variables in the univariate analysis including median age and sex were entered into a multivariate model using logistic regression analysis, and the odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Propensity score matching was calculated using the following parameters: age, sex, hypertension, lung disease, use of anti-cytokine therapies, baseline OSD and OSD during hospitalization.

The analysis was performed using the stepwise logistic regression model of the SPSS software package (SPSS version 23.0, SPSS Inc., Chicago, Illinois, USA). All statistical tests were 2-tailed, and the threshold of statistical significance was set at $p < 0.05$.

The Institutional Ethics Committee of the Hospital Clínic of Barcelona, approved the study and due to the nature of retrospective chart review, waived the need for inform consent from individual patients (Comité Ètic d'Investigació Clínica; HCB/2020/0273). All patients signed an informed consent for therapies off-label use.

Results

Two hundred and sixty-one patients were included in our study. Forty-one of them were SOT recipients, including 32 kidney recipients (78%), 4 liver recipients (10%), 3 heart recipients (7%) and 2 combined liver-kidney recipients (5%). Median follow-up was 68 days (IQR 57–75). Table 1 shows SOT recipients baseline characteristics. Median years from transplantation to COVID-19 diagnosis were 6 (range, 1–21). Fever was found in 95% (39) of the patients followed by cough in 68% (28) and dyspnoea in 32% (13). Two patients presented *Streptococcus pneumoniae* co-infection.

Table 2 shows the clinical characteristics and laboratory findings of transplant and non-transplant patients with COVID-19. We compared baseline characteristics of both groups. Hypertension was more frequent in transplanted patients compared to the non-transplant group (81% vs 45%, $p<0.001$), whereas diabetes mellitus was more frequent in the non-transplant group (32% vs 16%, $p = 0.01$). Transplant recipients had significantly more chronic kidney disease than non-transplant patients (34% vs 5% $p <0.001$). Dyspnoea and cough on admission were more frequent in the non-transplant group (57% vs 32%, $p = 0.003$; 82% vs 68%, $p = 0.032$). Median ferritin levels on admission were higher in the non-transplant group than in SOT recipients (776 vs 321, $p = 0.03$). Transplant patients had higher serum creatinine levels on admission than the non-transplant group ($p<0.001$). Regarding COVID-19 specific treatment, 23 transplant recipients received at least one anti-cytokine therapy (57%) that included tocilizumab, anakinra or baricitinib, compared to 125 (57%) of the non-transplant group ($p = 0.932$).

We found several differences in the complications during hospitalization; acute kidney injury was more frequent in the transplant group (49% vs. 16%, $p<0.001$). Persistent lymphopenia was more frequent in the transplant cohort compared to the non-transplant group ($p = 0.001$). Four cases of cryptogenetic organizing pneumonia were registered in the SOT group (10%) compared to 42 (19%) in the non-transplant group ($p = 0.1$). None of the SOT recipients was diagnosed with pulmonary embolism whereas it was diagnosed in 21 patients of the non-transplant group (0% vs 10%, $p = 0.04$). Transplant patients had longer hospital stay compared to the non-transplant group, almost reaching statistical significance (17 days vs 12, $p = 0.054$). There were no differences in terms of mortality between both groups (15% vs 12%, $p = 0.64$). Respiratory failure due to COVID-19 was the main cause of death in all patients

Table 1. Baseline characteristics of SOT recipients with COVID-19.

Variables	n = 41 (%)
Median age, years, IQR	58 (33–86)
Male sex	27 (66)
Transplanted organ	
Kidney	32 (78)
Liver	4 (10)
Heart	3 (7)
Combined liver-kidney transplant	2 (5)
Underlying conditions	
Hypertension	33 (81)
Diabetes mellitus	34 (83)
Cardiovascular disease	10 (24)
COPD	8 (20)
Chronic kidney disease	14 (34)
Years from transplant to diagnosis, median (IQR)	6 (1–21)
Immunosupressive regimen	
Calcineurin inhibitors based therapy	26 (63)
mTOR based therapy	15 (37)
Previous episodes of acute rejection (3 months, only biopsy proven)	0
COVID-19 adjuvant treatment	
Lopinavir/ritonavir	31 (76)
Hydroxychloroquine	40 (98)
Remdesivir	0
Azithromycin	41 (100)
Tocilizumab	19 (46)
Anakinra	7 (17)
Baricitimib	1 (2)
Steroids pulse	17 (41)
Interferon	3 (7)

*COPD: Chronic obstructive pulmonary disease.

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with the exception of a patient that died of complications of infective endocarditis. Fig 1 shows the Kaplan-Meier curve.

Table 3 shows clinical Ordinary Scale Determination on admission and during hospitalization by transplantation.

In terms of outcomes, 14 patients in the transplant group required ICU admission, of them 7 patients required mechanical ventilation (50%) and 5 died (12%). Ninety patients of the non-transplant group required ICU admission. Of them, 43 (20%) required mechanical ventilation and 33 died (15%).

Multivariate analysis of risk factors for mortality was performed and is depicted in Table 4. Older age (OR 1.142; 95% [CI 1.08–1.197]) higher levels of serum C-reactive protein (OR 3.068; 95% [CI 1.22–7.71]) and higher levels of serum creatinine on admission (OR 3.048 95% [CI 1.22–7.57]) were associated with mortality.

We performed a propensity score matching (PSM) including 36 patients in each group (Table 5).

Patients were matched one-to-one using PSM to eliminate confounding factors. Clinical variables entered into the PSM analysis were age, gender, comorbidities, biological therapy,

Table 2. Clinical characteristics and laboratory findings of transplant and non-transplant patients with COVID-19.

Variables	Transplanted n = 41 (%)	Non-transplanted n = 220 (%)	p
Age in years, median (IQR)	58 (33–86)	63 (51–72)	0.175
Male sex	27 (66)	144 (66)	0.961
Underlying conditions			
Hypertension	33 (81)	98 (45)	<0.001
Diabetes mellitus	34 (16)	13 (32)	0.013
Cardiovascular disease	10 (24)	29 (13)	0.065
COPD	8 (20)	38 (17)	0.730
Chronic kidney disease	14 (34)	11 (5)	< 0.001
Symptoms at admission			
Fever	39 (95)	201 (91)	0.417
Diarrhea	9 (22)	48 (22)	0.985
Dyspnoea	13 (32)	126 (57)	0.003
Cough	27 (68)	181 (82)	0.032
Median days from symptoms to diagnosis (IQR)	5 (2–9)	6 (4–8)	0.276
Laboratory values on admission, median (IQR)			
Lymphocyte (cell/mm)	600 (400–900)	800 (600–1000)	0.220
C-reactive protein (mg/dL) (NR<0)	9.4 (3–13.8)	8.1 (4.2–16.8)	0.479
D- dimer (ng/mL) (NR<500)	800 (600–2447)	800 (450–1400)	0.706
Lactate dehydrogenase (IU/mL) (NR<234)	289(400–900)	338 (264–424)	0.390
Creatinine, (mg/dL) (NR 0.3–1.3)	1.8 (1.2–2.9)	0.9 (0.7–1.09)	<0.001
Ferritin (ng /mL) (NR 20–400)	321 (264–949)	776 (391–1421)	0.030
Troponin (ng /mL) (NR <42.2)	8.2 (4.7–30.7)	11.2 (5.1–20.5)	0.551
COVID-19 adjuvant treatment			
Lopinavir/ritonavir	31 (76)	205 (93)	0.001
Hydroxychloroquine	40 (98)	216 (98)	0.390
Azithromycin	41 (100)	220 (100)	0.932
Tocilizumab	19 (46)	125 (57)	0.216
Anakinra	7 (17)	4 (2)	<0.001
Baricitinib	1 (2)	0	0.020
Remdesivir	0	29 (13)	0.005
Anti-cytokine therapy	23 (56)	125 (57)	0.932
Clinical outcomes			
Intensive care unit admission	14 (34)	90 (41)	0.317
• non-invasive ventilation	7 (17)	47 (21)	0.928
• mechanical ventilation	7 (17)	43 (19)	0.325
Complications			
Acute kidney injury	20 (49)	35 (16)	0.001
Other infection	10 (24)	26 (19)	0.462
Septic shock	5 (12)	51 (23)	0.110
Organizing pneumonia	4 (10)	42 (19)	0.150
Pulmonary embolism	0	21 (10)	0.04
Higher/lower* laboratory values during admission, median (IQR)			
Lymphocyte (cell/mm)	700 (500–1100)	1600 (1200–2300)	0.001
C-reactive protein (mg/dL)	14.4 (9–18.9)	15.5 (8.8–22.6)	0.754
D-dimer (ng/mL)	1300 (1000–4010)	2400 (1000–7600)	0.190
Lactate dehydrogenase (IU/mL)	367 (285–525)	448 (348–567)	0.027
Ferritin (ng /mL)	888 (442–1515)	1135 (648–1934)	0.161

(*Continued*)

Table 2. (Continued)

Variables	Transplanted n = 41 (%)	Non-transplanted n = 220 (%)	p
Troponin (ng/mL)	15.2 (7.1–52.0)	13.7 (6.3–31.2)	0.860
Median days of hospitalization (IQR)	17 (12–24)	12 (8–20)	0.054
Median days in ICU, median (IQR)	11 (7–22)	9 (5–15)	0.303
Mortality	5 (12.2)	33 (15)	0.640

* In case of C-reactive protein, D-dimer, lactate dehydrogenase, ferritin and troponin we selected the highest laboratory value during hospitalization. And in case of lymphocyte count we select the lowest laboratory value.

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categorical ordinal scale and mortality. There were no significant differences between matched groups in terms of mortality (14% vs 17%).

Discussion

In our study comparing a cohort of hospitalized SOT recipients with cohort of non-transplant recipients using a propensity score analysis we found no differences in mortality between the two groups. Therefore, in our cohort of patients with COVID-19, SOT cannot be considered a risk factor for mortality.

In our cohort of COVID-19 hospitalized patients, we found no differences in clinical presentation between SOT and non-transplant patients. However, the true incidence of COVID-19 infection and symptom development in SOT vs. general population remains to be established, due to the lack of universal testing in asymptomatic recipients. Ongoing seroprevalence studies may provide information on true infection incidence.

We did find differences in the use of COVID-19 specific therapy that was considered standard of care at the time of the study in the two groups. Transplant patients received significantly less lopinavir/ritonavir, and more anakinra compared to non-transplant patients. The important drug-drug interactions of lopinavir/ritonavir with immunosuppressant medications could have influenced physicians prescribing this drug [20]. Remdesivir which has been

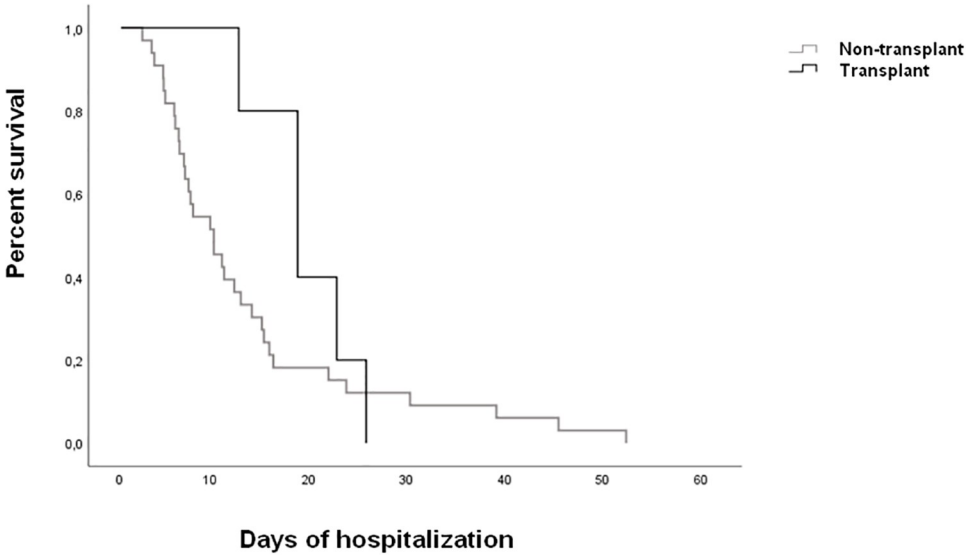

Fig 1. Kaplan-Meier analysis by transplant.

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Table 3. Ordinal Scale Determination at baseline, during hospitalization and at end of follow up by transplant.

Ordinal Scale Determination	Transplant n = 41 (%)	Non-transplant n = 220 (%)
Baseline		
Non-ICU[a] hospital ward, not requiring supplemental oxygen	25 (61)	63 (29)
Non-ICU hospital ward requiring supplemental oxygen	13 (32)	135 (61)
ICU or non-ICU hospital ward requiring non-invasive ventilation or high-flow oxygen	2 (5)	1 (1)
ICU, requiring intubation and mechanical ventilation	1 (2)	21 (10)
During hospitalization		
Non-ICU hospital ward, not requiring supplemental oxygen	9 (22)	-
Non-ICU hospital ward requiring supplemental oxygen	18 (44)	130 (59)
ICU or non-ICU hospital ward requiring non-invasive ventilation or high-flow oxygen	7 (17)	47 (21)
ICU, requiring intubation and mechanical ventilation or ECMO[b]	7 (17)	43 (20)
End of follow-up		
Discharged from hospital	36 (88)	189 (86)
Death	5 (12)	33 (15)

[a]ICU, intensive care unit;

[b]ECMO, *Extracorporeal membrane oxygenation*.

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shown to reduce the time to clinical improvement, was not administered to SOT patients, possibly as a result of higher incidence of chronic kidney disease and acute kidney injury, that contraindicate the use of this drug [21]. Randomized control trials with lopinavir/ritonavir and azythromycin as adyuvant therapy for COVID-19 have shown no benefit, and some have shown deleterious effects, and therefore they are no longer being used [22].

To the date, remdesivir and dexamethasone have shown to be beneficial in randomized controlled trials in the treatment of patients with COVID-19 [23–27]. Preliminary studies found promising results with the use of anakinra [28–32] and other anti-cytokine therapies [33–35], however, randomized controlled trials analyzing the use of these therapies the SOT population are lacking, with the special interest of development of opportunistic infections. In terms of complications during hospitalization, we found that acute kidney failure was more common in the transplant cohort, probably reflecting kidney function vulnerability of SOT recipients, and use of calcineurin inhibitors. Transplant patients had lymphopenia for a significantly longer time compared to non-transplant patients, possibly as a consequence of the use of drugs that cause myelotoxicity such as maintenance immunosuppressive therapy and prophylactic antibiotics. It is to be noted that despite having 25% patients with septic shock in the SOT group, compared to 12% in the non-transplant group, this did not influence the mortality significantly.

In the multivariate analysis of risk factors of mortality, solid organ transplantation was not associated with death. Our mortality rate is similar to other transplant cohorts [3,4,15]. However, other cohort have reported much worse outcomes, with mortality ranging from 28 to 67% [10,12]. These differences might me explained by demographic differences, including limited heath resources in the context of an overstretched health system in the peak of the pandemic. There have been several discussions around the impact of immunosupression on COVID-19 prognosis. It is reasonable to assume that during the viremic phase immunosuppressive therapy could potentially be deleterious, however, some studies have found that some drugs such as cyclosporine, tacrolimus and mTOR inhibitors [36] have in vitro activity against

Table 4. Univariate and multivariate analysis of risk factors associated with mortality.

				Univariate analysis		Multivariate analysis	
	Category	n	Mortality n (%)	OR (95% CI)	p value	OR (95% CI)	p value
Gender	Male	171	23 (13.5)				
	Female	90	15 (16.7)	1.287 (0.634–2.611)	0.484		
Age, years	< 63	137	4 (2.9)				
	> 63	124	34 (27.4)	12.561 (4.309–36.62)	<0.001	1.142 (1.089–1.197)	<0.001
Hypertension	Yes	131	27 (20.6)				
	No	130	11 (8.5)	2.809 (1.328–5.939)	0.005		
Cardiovascular disease	Yes	39	14 (35.9)				
	No	222	24 (10.8)	4.620 (2.119–10.073)	<0.001		
Chronic respiratory disease	Yes	46	13 (28.3)				
	No	215	25 (11.6)	2.994 (1.393–6.436)	0.004		
Solid Organ Transplantation	Yes	41	5 (12.2)				
	No	220	33 (15)	0.787 (0.288–2.152)	0.640		
serum C-reactive protein (mg/dL) Day 0	< 8.2	130	15 (11.5)				
	>8.2	131	23 (17.6)	1.633 (0.810–3.293)	0.168		
serum C-reactive protein (mg/dL), maximum value	< 15.2	130	8 (6.2)				
	>15.2	131	30 (23)	4.530 (1.989–10.318)	<0.001	3.068 (1.22–7.71)	0.017
serum Creatinine (mg/dL) Day 0	< 0.9	121	10 (8.3)				
	> 0.9	140	28 (20)	2.775 (1.287–5.983)	0.007	3.048 (1.226–7.575)	0.016
Lymphocytes (cell/mm3) Day 0	< 700	133	24 (18)				
	>700	128	14 (36.8)	0.558 (0.274–1.134)	0.104		
Serum ferritin (ng/mL) Day 0	< 749	124	14 (11.3)				
	>749	137	24 (17.5)	1.669 (0.821–3.393)	0.154		
D-dimer (ng/mL) Day 0	< 800	140	13 (9.3)				
	> 800	121	25 (20.7)	2.544 (1.237–5.230)	0.009		
Intensive care unit (ICU) admission	Yes	101	21 (20.8)				
	No	160	17 (10.6)	2.208 (1.101–4.427)	0.023		
Invasive mechanical ventilation	Yes	53	12 (22.6)				
	No	208	26 (12.5)	2.049 (0.955–4.395)	0.062		
Septic shock	Yes	56	14 (25)				
	No	203	23 (11.3)	2.609 (1.239–5.492)	0.010		
Biological therapy	Yes	148	18 (47.4)				
	No	113	130 (58.3)	0.644 (0.323–1.284)	0.209		
OSD[a], baseline							
Conventional ward, not requiring supplemental oxygen	Yes	88	5 (5.7)				
Conventional ward, requiring supplemental low-flow oxygen	Yes	148	25 (16.9)				
ICU[b], requiring supplemental high-flow supplemental oxygen	Yes	3	2 (66.7)				
ICU, requiring invasive mechanical ventilation/ECMO[c]	Yes	22	6 (27.3)	15.629	0.001		

[a]OSD, ordinary scale determination;

[b]ICU, intensive care unit.

[c]ECMO, *Extracorporeal membrane oxygenation*.

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other coronaviruses. Furthermore, immunosuppressive regimens might be beneficial preventing or in the event of a cytokine storm. Our cohorts median time from transplant was 6 years, with no documented recent episodes of rejection; and therefore not in the maximum period of immunosuppression.

Table 5. Comparison of transplant and non-transplant population after applying a propensity score matching.

Variables	Transplant n = 36 (%)	Non-transplant n = 36 (%)	p-value
Age in years, media (SD)	59.6 (13.2)	60.5 (12.7)	0.750
Male sex	11 (31)	13 (36%)	0.482
Underlying conditions			
Hypertension	28 (78)	29 (81)	0.693
Lung disease	8 (22)	7 (19)	0.693
Anti-cytokine therapy	18 (50)	20 (56)	0.514
Mortality	5 (14)	6 (17)	0.640

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Older age, maximum serum C-reactive protein and serum creatinine levels were associated with mortality. Older age has been related to worse prognosis in several studies [2,37–39]. C-reactive protein, a protein whose expression is driven by IL-6, is a biomarker of severe infection that has been associated with the inflammation cytokine storm related to COVID-19 [40].

Similarly, acute kidney injury has been associated with an increased risk of death in critically ill patients with pneumonia [41,42]. The SOT cohort also had significantly higher rate of chronic kidney disease, without having an impact on the overall mortality.

Our study has several strengths and limitations. We were able to analyze all consecutive admissions during the study period, being one of the first studies comparing transplant patients to non-transplant patients. However, there are several limitations; first of all, as it is a single-centre study, our findings may be attributable to institution-specific variables and secondly, it may not reflect the epidemiology of different centers and/or geographical areas, thus more extensive data are needed to confirm these results. In addition, given the small sample size of our study; we cannot exclude a type 2 error.

To conclude, the clinical course of SARS-CoV-2 infection in SOT recipients appears to be similar to that observed in the non-transplant population, even though COVID-19 specific treatment was different between SOT recipients and non-transplant patients. Older age, serum creatinine and C-reactive protein levels were associated with higher mortality. Solid organ transplant recipients did not experience worse outcomes.

Supporting information

S1 File.
(SAV)

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References

1. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report [Internet]. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200304-sitrep-44-covid-19.pdf?sfvrsn=783b4c9d_6.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3 PMID: 32171076
3. Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in Solid Organ Transplant Recipients: Initial Report from the US Epicenter. Am J Transplant. 2020; 20(7):1800–8. https://doi.org/10.1111/ajt.15941 PMID: 32330343
4. Tschopp J, L'Huillier A, Mombelli M, Mueller N, Khanna N, Garzoni C, et al. First experience of SARS-CoV-2 infections in solid organ transplant recipients in the Swiss Transplant Cohort Study. Am J Transplant. 2020; 20(10):2876–86. https://doi.org/10.1111/ajt.16062 PMID: 32412159
5. Ali T, Al-Ali A, Fajji L, Hammad E, Nazmi A, Alahmadi I, et al. Coronavirus Disease-19: Disease Severity and Outcomes of Solid Organ Transplant Recipients: Different Spectrums of Disease in Different Populations? Transplantation. 2021. https://doi.org/10.1097/TP.0000000000003433 PMID: 32852405
6. Favà A, Cucchiari D, Montero N, Toapanta N, Centellas FJ, Vila-Santandreu A, et al. Clinical characteristics and risk factors for severe COVID-19 in hospitalized kidney transplant recipients: A multicentric cohort study. Am J Transplant. 2020. https://doi.org/10.1111/ajt.16246 PMID: 32777153
7. Mehta SA, Leonard J, Labella P, Cartiera K, Soomro I, Neumann H, et al. Outpatient management of kidney transplant recipients with suspected COVID-19—Single-center experience during the New York City surge. Transpl Infect Dis. 2020. https://doi.org/10.1111/tid.13383 PMID: 32578324
8. Demir E, Uyar M, Parmaksiz E, Sinangil A, Yelken B, Dirim AB, et al. COVID-19 in kidney transplant recipients: A multicenter experience in Istanbul. Transpl Infect Dis. 2020. https://doi.org/10.1111/tid.13371 PMID: 32657540
9. Caillard S, Anglicheau D, Matignon M, Durrbach A, Greze C, Frimat L, et al. An initial report from the French SOT COVID Registry suggests high mortality due to COVID-19 in recipients of kidney transplants. Kidney Int. 2020; 98(6):1549–58. https://doi.org/10.1016/j.kint.2020.08.005 PMID: 32853631
10. Fernández-Ruiz M, Andrés A, Loinaz C, Delgado JF, López-Medrano F, San Juan R, et al. COVID-19 in solid organ transplant recipients: a single-center case series from Spain. Am J Transplant. 2020; 20(7):1849–58. https://doi.org/10.1111/ajt.15929 PMID: 32301155

11. Latif F, Farr MA, Clerkin KJ, Habal MV., Takeda K, Naka Y, et al. Characteristics and Outcomes of Recipients of Heart Transplant with Coronavirus Disease 2019. JAMA Cardiol. 2020; 13(e202159). https://doi.org/10.1001/jamacardio.2020.2159 PMID: 32402056

12. Abrishami A, Samavat S, Behnam B, Arab-Ahmadi M, Nafar M, Sanei Taheri M. Clinical Course, Imaging Features, and Outcomes of COVID-19 in Kidney Transplant Recipients. Eur Urol. 2020; 78(2):281–6. https://doi.org/10.1016/j.eururo.2020.04.064 PMID: 32409114

13. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int. 2020; 97(6):1083–8. https://doi.org/10.1016/j.kint.2020.04.002 PMID: 32354634

14. Hoek RAS, Manintveld OC, Betjes MGH, Hellemons ME, Seghers L, van Kampen JAA, et al. Covid-19 in solid organ transplant recipients: A single center experience. Transpl Int. 2020; 33(9):1099–105. https://doi.org/10.1111/tri.13662 PMID: 32460390

15. Travi G, Rossotti R, Merli M, Sacco A, Perricone G, Lauterio A, et al. Clinical outcome in solid organ transplant recipients with COVID-19: A single-center experience. Am J Transplant. 2020; 20(9):2628–9. https://doi.org/10.1111/ajt.16069 PMID: 32436646

16. Cravedi P, Mothi SS, Azzi Y, Haverly M, Farouk SS, Pérez-Sáez MJ, et al. COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium. Am J Transplant. 2020; 20 (11):3140–8. https://doi.org/10.1111/ajt.16185 PMID: 32649791

17. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and Kidney Transplantation. N Engl J Med. 2020; 382(25):2475–7. https://doi.org/10.1056/NEJMc2011117 PMID: 32329975

18. Mamode N, Ahmed Z, Jones G, Banga N, Motallebzadeh R, Tolley H, et al. Mortality Rates in Transplant Recipients and Transplantation Candidates in a High-prevalence COVID-19 Environment. Transplantation. 2021; 105(1):212–5. https://doi.org/10.1097/TP.0000000000003533 PMID: 33196624

19. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 Apr 22; 323(20):2052–9. https://doi.org/10.1001/jama.2020.6775 PMID: 32320003

20. Aslam S. Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic. https://ishlt.org/ishlt/media/documents/SARS-CoV-2_-Guidance-for-Cardiothoracic-Transplant-and-VAD-centers.pdf.

21. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395(10238):1694. https://doi.org/10.1016/S0140-6736(20)31022-9 PMID: 32423584

22. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo A-M, Preziosi M-P, Sathiyamoorthy V, et al. Repurposed Antiviral Drugs for Covid-19—Interim WHO Solidarity Trial Results. N Engl J Med. 2020.

23. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. JAMA—J Am Med Assoc. 2020; 324(11):1048–57. https://doi.org/10.1001/jama.2020.16349 PMID: 32821939

24. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients with Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA—J Am Med Assoc. 2020; 324 (13):1307–16. https://doi.org/10.1001/jama.2020.17021 PMID: 32876695

25. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020; 8(3):267–76. https://doi.org/10.1016/S2213-2600(19)30417-5 PMID: 32043986

26. Sterne JAC, Murthy S, Diaz J V., Slutsky AS, Villar J, Angus DC, et al. Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis. JAMA—J Am Med Assoc. 2020; 324(13):1330–41. https://doi.org/10.1001/jama.2020.17023 PMID: 32876694

27. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19—Final Report. N Engl J Med. 2020; 383(19):1813–26. https://doi.org/10.1056/NEJMoa2007764 PMID: 32445440

28. Dimopoulos G, de Mast Q, Markou N, Theodorakopoulou M, Komnos A, Mouktaroudi M, et al. Favorable anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis. Cell Host Microbe. 2020; 28(1):117–23. https://doi.org/10.1016/j.chom.2020.05.007 PMID: 32411313

29. Aouba A, Baldolli A, Geffray L, Verdon R, Bergot E, Martin-Silva N, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis. 2020; 79(1):1381–2. https://doi.org/10.1136/annrheumdis-2020-217706 PMID: 32376597

30. Day JW, Fox TA, Halsey R, Carpenter B, Kottaridis PD. IL-1 blockade with anakinra in acute leukaemia patients with severe COVID-19 pneumonia appears safe and may result in clinical improvement. Br J Haematol. 2020; 190(2):e80–3. https://doi.org/10.1111/bjh.16873 PMID: 32438450

31. Filocamo G, Mangioni D, Tagliabue P, Aliberti S, Costantino G, Minoia F, et al. Use of anakinra in severe COVID-19: a case report. Int J Infect Dis. 2020; 96:607–9. https://doi.org/10.1016/j.ijid.2020.05.026 PMID: 32437934

32. Franzetti M, Pozzetti U, Carugati M, Pandolfo A, Molteni C, Faccioli P, et al. Interleukin-1 receptor antagonist anakinra in association with remdesivir in severe Coronavirus disease 2019: A case report. Int J Infect Dis. 2020. https://doi.org/10.1016/j.ijid.2020.05.050 PMID: 32422376

33. Colaneri M, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F, et al. Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE). Microorganisms [Internet]. 2020 May 9 [cited 2020 May 24]; 8(5). Available from: http://www.ncbi.nlm.nih.gov/pubmed/32397399.

34. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev [Internet]. 2020 May 3 [cited 2020 May 24];102568. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32376398. https://doi.org/10.1016/j.autrev.2020.102568

35. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci [Internet]. 2020 May 19 [cited 2020 May 24]; 117(20):10970–5. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.2005615117. PMID: 32350134

36. Tanaka Y, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. Viruses. 2013; 5(5):1250–60. https://doi.org/10.3390/v5051250 PMID: 23698397

37. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ. 2020; 386:m1091. https://doi.org/10.1136/bmj.m1091 PMID: 32217556

38. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(7):811–8. https://doi.org/10.1001/jamacardio.2020.1017 PMID: 32219356

39. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; 5(7):802–10. https://doi.org/10.1001/jamacardio.2020.0950 PMID: 32211816

40. Moore BJB, June CH. Cytokine release syndrome in severe COVID-19. Science (80-). 2020; 368 (6490):473–4. https://doi.org/10.1126/science.abb8925 PMID: 32303591

41. Li G, Cook DJ, Thabane L, Friedrich JO, Crozier TM, Muscedere J, et al. Risk factors for mortality in patients admitted to intensive care units with pneumonia. Respir Res. 2016; 17(1):80. https://doi.org/10.1186/s12931-016-0397-5 PMID: 27401184

42. Rodriguez A, Lisboa T, Blot S, Martin-Loeches I, Solé-Violan J, De Mendoza D, et al. Mortality in ICU patients with bacterial community-acquired pneumonia: When antibiotics are not enough. Intensive Care Med. 2009; 35(3):430–8. https://doi.org/10.1007/s00134-008-1363-6 PMID: 19066850